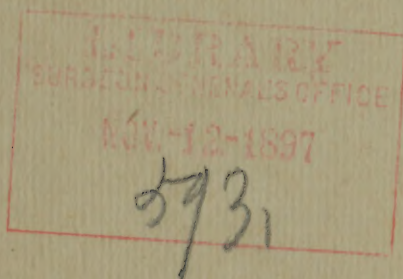


Woodbury (Fr.)

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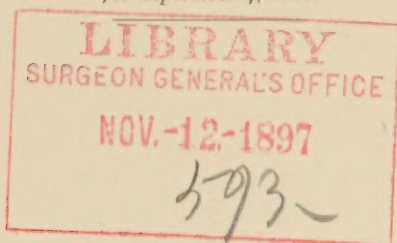
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A NOTE ON TWO NEW CREOSOTE COMPOUNDS  
CREOSOTE VALERIANATE  
AND GUAIACOL VALERIANATE.\*

BY FRANK WOODBURY, M. D.,  
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IN these days of new remedies of ephemeral usefulness and evanescent reputation, it is refreshing to take up for brief consideration a drug with an established record of more than half a century. We recall the fact that while experimenting with tar from beech wood, Reichenbach, in 1832, first obtained a fluid substance which, on account of its possessing preeminently the power of preventing putrefaction in organic substances, he termed "creosote," or "flesh preserver." That expert chemist also fully recognized the fact that the new chemical agent was not a simple but a very complex substance, being composed principally of hydrocarbons of the aromatic group. It also contains a variable quantity of water. According to a recent authority, Marasse, it contains phenol, cresol, phlorol, guaiacol, and creosol; also methylecresol, and the methylic ethers of guaiacol,

\* Read before the Section in Materia Medica, Pharmacy, and Therapeutics of the American Medical Association, June 3, 1897.

phlorol, etc. By fractional distillation, Hofmann separated the dimethylic ethers of pyrogallol, of methyl pyrogallol, and of propyl pyrogallol, from that portion of the creosote which passes over at a temperature above  $220^{\circ}$ . Hofmann discovered a new body, which he named cœrulignol, which possesses powerful toxic properties and which should be carefully removed from creosote that is to be used for medicinal purposes. Its presence may be detected by treating an alcoholic solution of creosote by a test solution of barium hydrate. If cœrulignol is present the solution will turn blue or show a bluish tinge. Benzine may be substituted for alcohol, with the same result. The United States Pharmacopœia has adopted this as one of the tests indicating the suitability of a specimen of creosote for medicinal use.

I have referred to the early studies of creosote by its discoverer, Reichenbach, in order to bring into marked prominence the fact that it was first obtained from tar from the beech wood, and the early experiments made upon this agent, not only chemically, but also physiologically and clinically, were made with this form of creosote, which is still considered the best for medical use, and which is now used almost exclusively in therapeutics. An analogous substance obtained from coal tar is simply a mixture of phenol and cresylol of variable composition, or, in other words, an impure carbolic acid. They differ chemically principally in the following characters: Creosote from wood tar, added to an equal quantity of glycerin, is precipitated upon the addition of water; added to collodion, it does not coagulate it; and when treated with nitric acid and heat, by Clarke's method, yields oxalic acid. The so-called creosote from coal tar is not precipitated by water from its gelatin so-

lution; it does coagulate collodion, and yields picric acid when treated with nitric acid. There are corresponding and equally well-marked differences between the two compounds in their physiological action, the most important being the comparative innocuousness of pure wood-tar creosote, which can be taken in large doses, not only without toxic symptoms, but with decided therapeutic results.

It has unfortunately occurred that for many years the coal-tar compound was frequently dispensed for creosote, and the latter consequently fell into disrepute for a time on account of the accidents and untoward results from its use. Creosote, according to Dr. H. C. Wood, also, is liable to be adulterated with eupion. In the last edition of the *United States Dispensatory*, by Professors Wood, Remington, and Sadtler, the statement is made that "commercial creosote almost always contains carbolic and cresylic acids from coal tar; and, indeed, much of what is sold for creosote is nothing more than impure carbolic acid." I can not, however, agree with these distinguished authorities in the statement contained in the sentence immediately following the above, which says, referring to carbolic acid, that "this acid strongly resembles creosote, and this resemblance probably extends also to their therapeutical effects, so that the substitution is less to be regretted than might otherwise be the case." This I regard as a most misleading and dangerous teaching. A patient may take as much as six hundred drops of creosote, as in Dr. Freudenthal's case (*Medical Record*, 1892), and recover practically without the use of any antidote; but would this case have resulted so favorably had the same quantity of carbolic acid been swallowed instead of creosote?

The principal constituent of creosote is guaiacol, the methyl ether of pyrocatechin, which is said to be present in the proportion of sixty to eighty per cent. in the best specimens. Guaiacol, in a pure state, is crystalline, but as commonly met with is an oily-looking fluid with a peculiar pungent, smoky odor. It can be obtained, however, in an absolutely pure condition from a commercial sample, by cooling with a mixture of ice and salt, and then separating the crystals which have formed, as stated by S. Winghoffer (*Pharmaceutische Zeitung*, Berlin, 1894).

On account of the liability to adulteration in commercial guaiacol and its variable composition, various compounds have been introduced into the practice of medicine as substitutes for creosote and guaiacol. Among the more prominent of these are the carbonate of guaiacol; guaiacol salol, benzoyl guaiacol, or benzosol; cinnamyl guaiacol, or styracol; guaiacol phosphite, guaiacol biniodide, and most recently the guaiacol valerianate, or geosot. These various compounds are administered with the view of their undergoing decomposition in the intestinal tract and yielding guaiacol at the point where it can be most readily absorbed into the blood-vessels. In this way the administration of chemically pure guaiacol is accomplished more surely than by any other method. Moreover, these compounds, generally speaking, are more agreeable to the palate than the guaiacol itself.

*Chemistry.*—The following is Dr. Wendt's process for the manufacture of the valerianic-acid esters of creosote, eosote, and geosote:

The description of the process of manufacture and of the physical and chemical properties of these esters

can properly be confined for the purpose in question to the esters of the two most important constituents of the wood-tar creosote, the guaiacol and creosol.

To fifteen parts of creosol and twenty parts of valerianic acid seven parts of oxychloride of phosphorus are to be added. The mixture is then gently heated and boiled for the beginning in the water bath, and later on the open flame, until the development of hydrochloric acid has ceased. Afterward the mixture is washed with a three-per-cent. solution of caustic soda, well shaken with benzol, separated from the solvent medium and from water.

The ester represents an indifferent, slightly yellow, oily liquid, and boils in the vacuum (two to three millimetres pressure) between  $117^{\circ}$  and  $121^{\circ}$  C. The creosol used in the process is distilled in vacuum (two to three millimetres pressure) for the greater part between  $81^{\circ}$  to  $85^{\circ}$  C.

The ester is easily soluble in alcohol, ether, and benzole, and has an aromatic odor.

The process for the manufacture of guaiacol valerianate (geosote) is slightly different:

Five parts of guaiacol are mixed with seven parts and a half of chloride of valeryl and gently heated until boiling occurs, at first over the water bath and later on the open flame, and until the development of hydrochloric acid ceases. Then the mixture is washed with a cold three-per-cent. solution of caustic soda, diluted with benzol, separated from the solvent medium, and exsiccated.

The physical and chemical properties of this ester are practically the same as those of the analogous creosol ester. The boiling point of both of them under the

regular atmospheric pressure is stated to be about 260° C. Other compounds of the esters resulting from the process of esterification of commercial creosote with valerianic acid begin to distill at a temperature of about 240° C.

*Physiological Action.*—The valerianic-acid esters of the wood-tar creosote, especially of the most important constituents—that is, of guaiacol and creosol—are distinguished by their special property of being easily absorbed by the human system, and particularly by the fact that the heart and nerve tonic property of the valerianic acid is entirely preserved in these preparations.

Locally, guaiacol acts like solutions of carbolic acid to produce limited surface anæsthesia. Dr. Newcomb, of New York, at the recent meeting of the American Laryngological Association, recommended a five-per-cent. solution in olive oil as a substitute for cocaine for nasal operations. I have myself used the guaiacol valerianate for this purpose, both in full strength and diluted, and found it to possess, after a slight sensation of heat, decided anæsthetic effects, which are slower in appearing than after the application of cocaine, and which are not followed by secondary hyperæmia. The antiseptic power of guaiacol is also of great value in throat and nose operations. We know of the frequency of the presence of virulent bacilli in the nasal chambers of apparently healthy individuals, and the routine use of detergent remedies, followed by a decided antiseptic, such as guaiacol in oily solution, or the more agreeable valerianate of guaiacol, is now almost necessary in the conduct of our hospital and private work. I should have stated that the valerianate has a strong odor of valerian, which al-

most masks the guaiacol, and produces a combination the odor of which is suggestive of walnuts. Guaiacol valerianate is a local anæsthetic to the skin when applied in full strength.

The temperature-reducing power of guaiacol, discovered by Sciolla in 1894,\* is one of the most remarkable observations in the whole realm of pharmacology. This is not likely to occur in persons of good health with a normal temperature, but it is very marked in conditions of pyrexia. Caporali † has found that the external applications of guaiacol not only relieve pain and reduce abnormal temperature, but also increase the utilization of albuminoids by the organism and the absorption of fat and diminish oxidation.

Administered internally, guaiacol and creosote both exert a powerful antiseptic action upon the contents of the alimentary canal. The temperature reduction appears to be due to a special action of guaiacol upon the peripheral end organs of the nerves in the skin and mucous membranes. Upon the heart and blood-vessels there are no obvious effects from moderate doses of creosote or guaiacol. In larger doses it acts as a cardiac depressant, producing diaphoresis from relaxation of the blood-vessels, also giddiness and a tendency to fainting or collapse, convulsions, or coma, but these disagreeable effects are more likely to occur from commercial creosote or guaiacol than from a chemically pure article. In escaping from the blood by the bronchial mucous membrane and urinary organs, guaiacol exerts a local stimulant and antiseptic action.

\* *Cronica di clin. med. di Geneva* for 1894, vol. i, p. 171.

† *Riforma medica*, Naples, No. 175, 1894.

From this very brief review of the physiological action of guaiacol I turn to the therapeutic use.

As my time is limited, I will confine my remarks to the guaiacol valerianate and creosote valerianate (for brevity, denominated eosote and geosote) which were recently introduced by Dr. Gustav Wendt, of Berlin, and which I have used, to some extent, for the past three months in private and dispensary practice. For the same reason I will omit notes of cases, and simply summarize some of the results of the use of these agents. Both of them are liquid and have characteristic odors, the guaiacol valerianate being more agreeable to patients than the creosote compound.

In painful affections of the skin, attended by hyperæmia, such as inflamed acne, or abscess in the external auditory canal, pin boils, etc., applications of pure guaiacol valerianate (geosote) relieved pain and checked further pus formation. In chilblains this agent promptly relieved the annoying symptoms. Small compresses wet with guaiacol and applied over the painful spots of Vallein afford almost immediate relief in neuralgia.

In an acute erythema of the face, apparently erysipelatous, but possibly the result of rhus poisoning, a single application of this agent for ten minutes, followed by applications of zinc ointment containing creosote (one drachm to the ounce), afforded immediate relief and prompt disappearance of the inflammation. In the cases of children, however, or where larger areas are involved, the antithermic effect should be borne in mind, and not more than twenty-five to thirty drops applied at one time. I have already alluded to the use of guaiacol valerianate in the treatment of affections of the nose. In acute rhinitis it should be diluted with three or more

parts of oil of sweet almonds, or liquid albolene, and in this form it acts as a protective as well as an analgetic and antiseptic application. In chronic rhinitis, especially the purulent form, as well as in some varieties of atrophic rhinitis, it is used in full strength with advantage, as many of these cases are kept up by the presence of virulent micro-organisms, the action of which is inhibited by the guaiacol. In ulcerated conditions, even of supposed tuberculous origin, a few applications of pure guaiacol or creosote valerianate materially promote the healing process, at the same time relieving pain. This observation also applies to the larynx. I have not yet employed it in lupus, but it might be of service here for its local anæsthetic effects, prior to scraping and the application of lactic acid and the subsequent use of a twenty-per-cent. guaiacol spray, as recommended by Dr. P. Watson Williams.\* In tuberculosis of the air-passages external applications of pure guaiacol have been recommended by Dr. J. Solis-Cohen and others, and for this purpose the valerianate (geosote) would have especial advantage. Internally, guaiacol valerianate is given either in milk or dilute alcohol, or, better, in the form of capsules. It checks bronchorrhœa and reduces the number of tubercle bacilli in the sputum, at the same time that it tends to prevent reinfection from the intestinal tract. It is well borne in moderate doses, ten to thirty minims daily, or one to three capsules, each containing two grains, or three minims and a third, three times a day.

In the treatment of gastric catarrh, chronic gastritis with gastrectasia, and other conditions associated with or producing fermentation of the contents of the stomach, I have used creosote valerianate (eosote) in prefer-

\* *Medical Annual*, London, 1897.

ence to the guaiacol valerianate (geosote), as I believe it to exert stronger antiseptic action. It also overcomes nausea, and in connection with lavage favors return to a healthy condition of the mucous membrane and the reestablishment of appetite and normal digestion.

Fifty years ago Dr. Falmestock \* used pure creosote as an application to erysipelas with remarkable success. I have already referred to the use of guaiacol valerianate as a local application for erythema, and would suggest its use as a topical agent in erysipelas and also in small-pox.

In cases of pulmonary phthisis the remedy has been well borne, but I have had it too brief a time under observation to report decided results. Very favorable results, however, have been observed by Dr. Rieck, of Bassum, Germany,† who reports increase of appetite and powers of digestion, and of physical strength under its use. In cases of the initial stage of tuberculosis of the lungs this improvement was quite marked, with a decided diminution of the cough; the expectoration not only became more free, but it also decreased steadily in quantity. The night sweats disappeared.

This report was based upon the study of twenty-three cases (sixteen of catarrh of the apices and seven of developed tuberculosis) which were markedly benefited.

I have found the guaiacol valerianate (geosote) of decided value in the treatment of the so-called catarrhal state which is sometimes considered as the pre-tuberculous stage of phthisis pulmonalis. It seems especially

\* *American Journal of the Medical Sciences*, 1848.

† *Deutsche Medicinal-Zeitung*, Berlin, December 24, 1896.

suited, when properly diluted with some bland oil, for intratracheal injection in cases of advanced phthisis with or without ulceration in the larynx or cavity in the lung.

Inhalation of creosote in combination with oil of peppermint is alleged by Dr. Carasso to cause a disappearance of the tubercle bacilli from the sputum, and he reports good results, clinically, after nearly ten years' experience with it. Certainly this form of aerial medication is worthy of extended trial, and guaiacol valerianate would be preferable to creosote for this purpose.

I am of the opinion that in guaiacol we have the best remedy known at present to counteract the pernicious activity of the tubercle bacillus, and I may repeat the words of Dr. Jacobi: "No one treatment of all forms of tuberculosis ever satisfied me to the same degree as has that of guaiacol." When introduced into the stomach the guaiacol valerianate is decomposed and the effects of pure guaiacol, with the sedative action of valerianic acid, are obtained simultaneously, which may be expected to have a favorable effect upon the nervous manifestations of the disease, reducing cough and restlessness. In pneumonia, Malderesco used applications of guaiacol to the thorax, posteriorly, over the affected area of lung, with reduction of temperature and a diminished mortality.

I have thought that these few notes on a recent form of an old remedy might be of interest to the members of the section, and I beg to present, for their inspection, samples of the guaiacol valerianate (geosote) and creosote valerianate (eosote), the valerianic-acid esters of guaiacol and of creosote respectively. For further and

more detailed information I may refer those interested to reports from the medical clinic of the Royal Charity Hospital, of Berlin, by Dr. Grawitz, and of Dr. Rieck, already referred to, which have appeared in the *Deutsche Medizinal-Zeitung* and the *Therapeutische Monatshefte* for 1896.



